

*Remarks/Arguments*

**I. Status of the Claims:**

Claims 1, 11 and 31 are amended herein and new claims 36 and 37 are added herein. Support for the amendments and new claims can be found, *inter alia*, at page 4, line 6 through page 5, line 19, of the specification. The amendments do not add new matter. Claims 1-15 and 17-37 are pending in the application.

**II. Specification**

The Examiner has objected to the specification for the lack of headings, improper use of Trademarks and inclusion of hyperlinks. Applicants have amended the specification to address the Examiner's concerns and respectfully request the amendments be entered into the record.

**III. Rejections Under 35 U.S.C. § 112, second paragraph**

Claims 1-10 and 31-35 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants respectfully disagree but have amended the claims to advance prosecution.

The Examiner asserts that the claims are unclear as to whether the same computer is used for each of the steps in the claims. Applicants have amended claims 1 and 31 to recite "the" computer instead "a" computer for all of the steps after the initial step. Applicants believe the amended claims are in full compliance with the requirements of 35 U.S.C. § 112, second paragraph.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112.

**IV. Rejections Under 35 U.S.C. § 103**

Claims 1-15 and 31-35 stand rejected under 35 U.S.C. § 103, as being unpatentable over Hoover *et al.* (Nucleic Acids Research, 30(10): e43, 2002) ("Hoover"). Applicants respectfully disagree but have amended claims to advance prosecution.

The Examiner asserts that Hoover discloses a method and system for automated designing oligonucleotides based on the amino acid sequence of a protein/peptide. When the algorithm of Hoover is compared to the method of the present claims, a number of differences are apparent.

In the present invention, optimization positions are specified, i.e. in every iteration the sequence is mutated only at the specified optimization positions, which are a subset of the codons to be optimized, not at random codons and at randomly selected positions of the entire sequence as in Hoover.

In Hoover, the result of an iteration is not necessarily the sequence with the best score, but can be a sequence with a worse score than a previous sequence with a likelihood that is determined by a Boltzmann distribution. In contrast, in the presently claimed invention the codons chosen as result codons, i.e. those codons that are not varied in subsequent iterations and thus form part of the final optimized sequence are chosen from the optimal test sequence found in an iteration. According to Hoover's algorithm, in every iteration the sequence is either maintained as a whole or rejected as a whole, but never maintained in part as in the present invention.

In addition, Hoover discloses a global optimization approach while the present invention is directed to a more localized optimization approach. From a biological perspective the sequence properties which influence its technical usefulness (e.g. maximal expression of the encoded protein in a host organism) are less global properties (like the overall GC content) but much more local features (e.g. the GC content within a window of 40 base pairs or the presence/absence of a certain sequence motif, which may influence the expression). The present invention addresses this issue by looking at only a subpart of the sequence within one iteration and finding the best possible solution for this part with a non-stochastic approach, e.g. by doing an exhaustive search for the optimal subsequence. After the optimal subsequence is determined it is not changed in later iterations.

The determination of result codons which are not changed in later iterations is not suggested or disclosed by Hoover. In the present invention, once the optimal occupation of the  $m$  optimization positions is found, a number ( $p$ ) of these optimal codons are fixed as result codons and are not changed in the course of further iterations. This means that in subsequent iterations of the algorithm the  $m$  optimization positions will be different from previously established result codons. In other words the presently claimed process employs a kind "memory" to preserve the optimal solution for a subpart of the whole sequence throughout further iterations. In contrast, the only information Hoover's approach saves unalterably throughout the multiple iterations is the quality score of the sequence generated in the last iteration immediately before the current iteration. Hoover's method randomly varies codons in different iterations.

The Examiner asserts that in the present invention, the specified position to be optimized is  $m$ , but  $m$  could be equal to  $n$ , which is the number of codons and the latter could be equal to  $N$ , which is the number of amino acids in the entire protein sequence. (Office Action, page 10.) Applicants note that the claims recite in part "specifying, using the suitably programmed computer,  $m$  optimization positions in the test sequence which correspond to the position of  $m$  codons at which the occupation by a codon, relative to the test sequence, is to be optimized, where  $m \leq n$  and  $m < N$ " which clearly indicates that  $m$  is smaller than  $N$  and that  $m$  optimization positions cannot be equal to  $N$ . Further, Applicants have amended the claims to recite "where  $n$  is a natural number and is less than or equal to  $N$ ." Applicants assert that the present

claims are clearly distinguished from Hoover where m is equal to N. Because Hoover does not disclose all of the limitations of the claims a *prima facie* case of obviousness has not been established.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

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### **CONCLUSION**

The extendable due date for response to the instant Office Action, under a three-month shortened statutory period, is **June 22, 2011**. Applicants do not believe that any additional fees are due in connection with this Response. However, in the unlikely event that any such fees are due, the Commissioner is hereby authorized to charge the same to Deposit Account No. 50-3994, with reference to our matter LT00379 US. This is not an authorization to pay the issue fee.

Applicants respectfully request that this paper be entered. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application and the pending claims as amended are now in condition for. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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